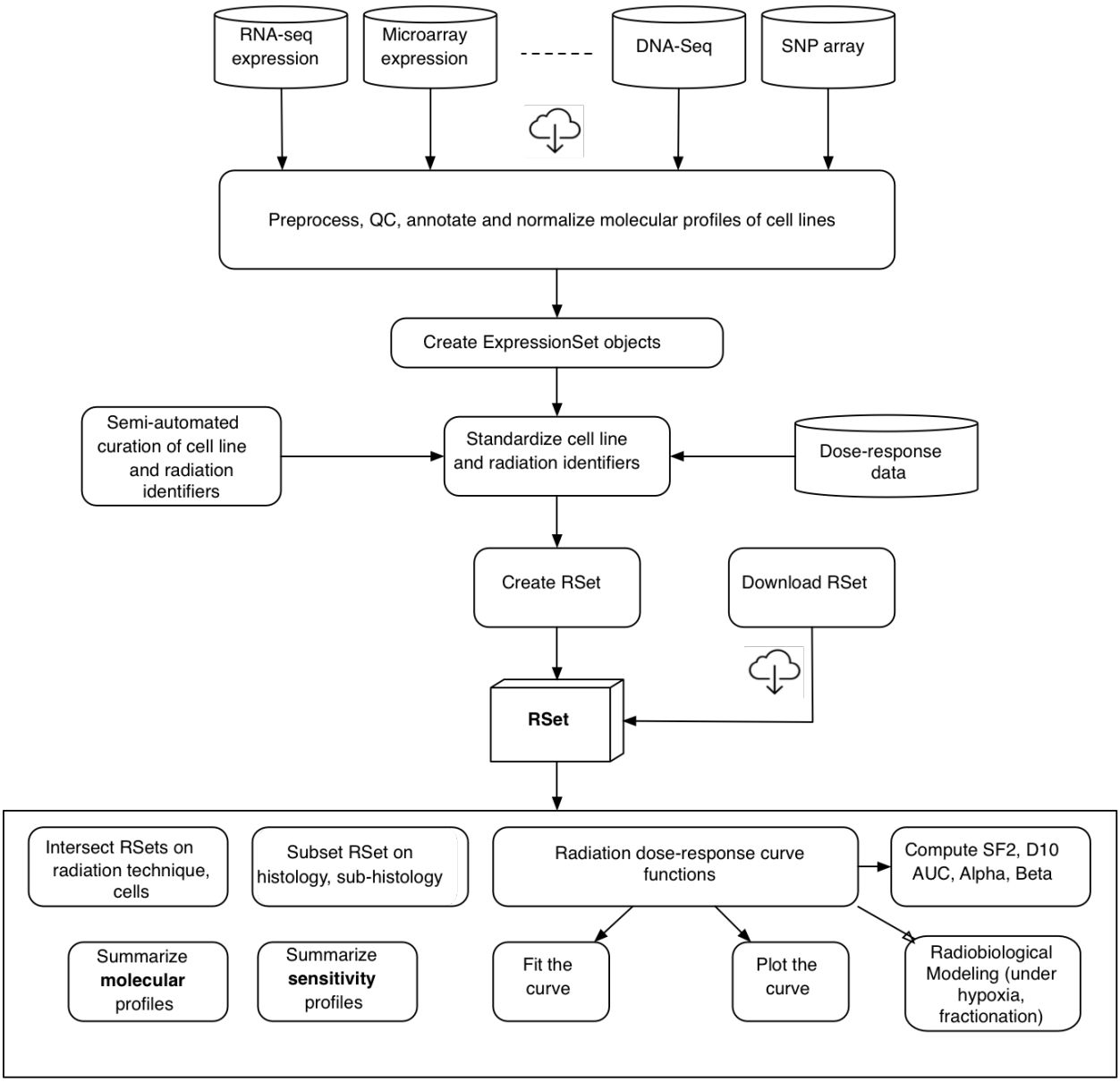
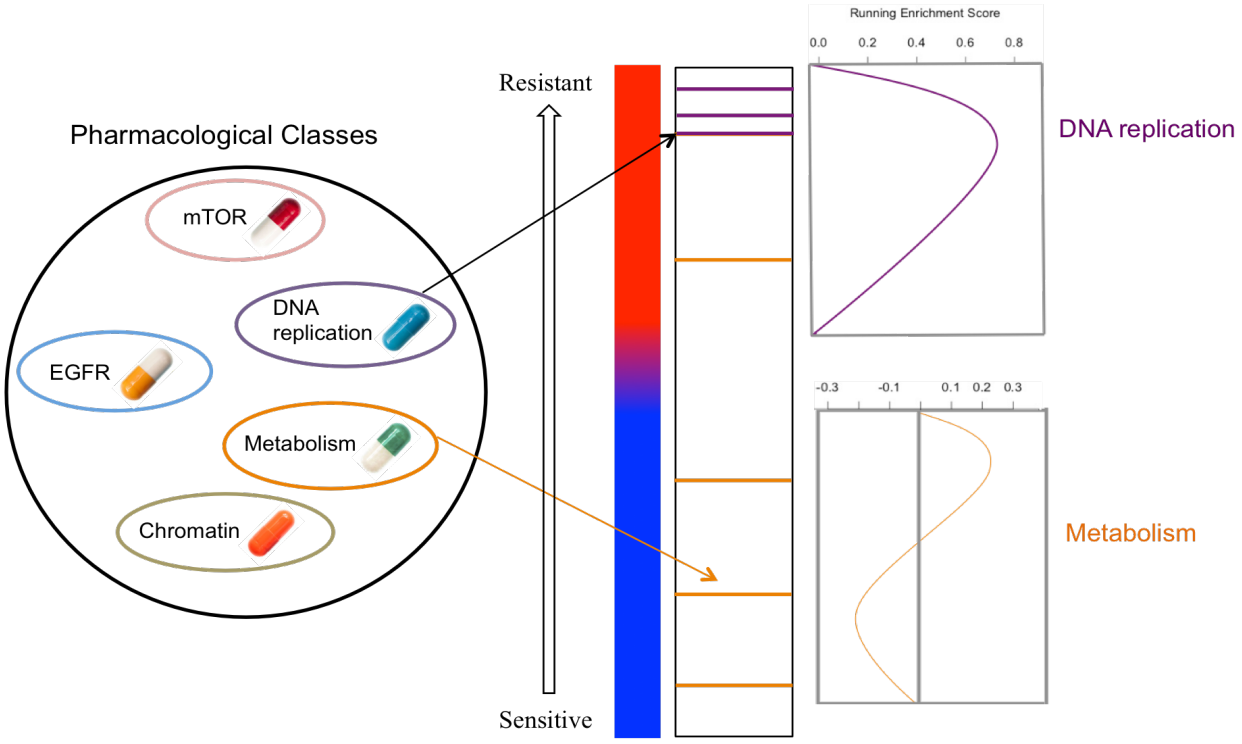
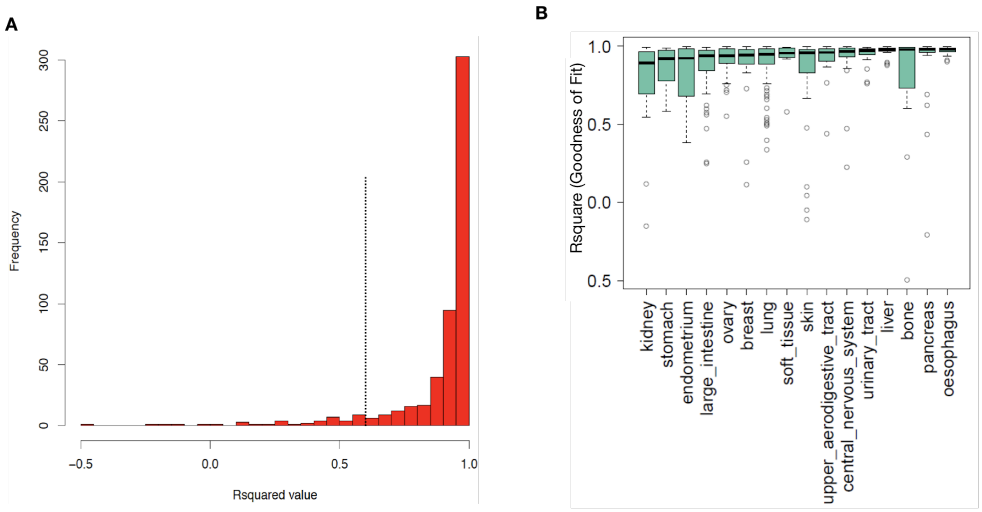


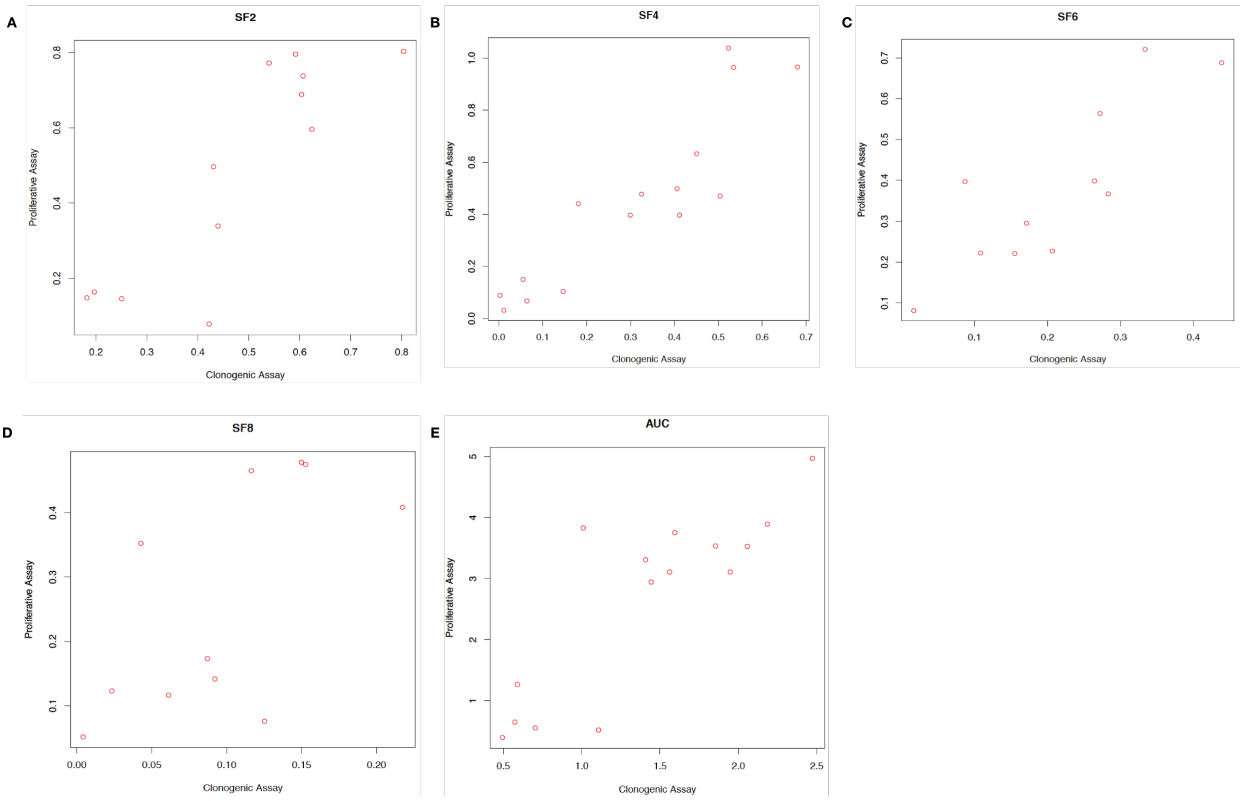
Supplementary Figure 1: Design of RadioGx. The figure illustrates the main steps required to create RadioSet (RSet) objects and the functions implemented in the package to leverage the curated radiogenomic datasets. The molecular data and radiation dose response data are presented as cylinders; these data sets can be downloaded from the project website and related repositories (illustrated by the cloud icon). The cell line names are standardized and linked to the molecular and radiogenomic profiles to create an RSet object, which is available through the function downloadRSet. Functions to fit the radiation dose response data, visualize them, and compute SF2/AUC/etc. are available. Finally, users can also model the effects of radiation response under various conditions (e.g., hypoxia). A complete reference manual is available from CRAN.



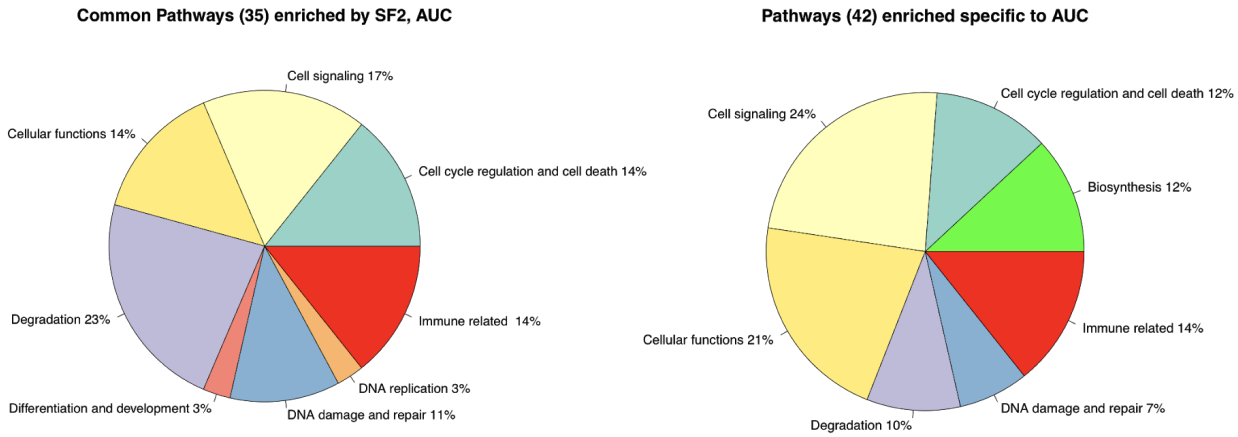
Supplementary Figure 2: PCL enrichment analysis methodology. Schematic describing the pharmacological (PCL) enrichment analysis methodology. This method is adapted from the gene set enrichment analysis (GSEA) where gene sets are replaced by sets of pharmacological classes of drugs. For illustrative purposes, DNA replication pharmacological class is shown to be positively enriched according to changes in AUC, while the metabolism is pharmacological class is not enriched according to changes in AUC.



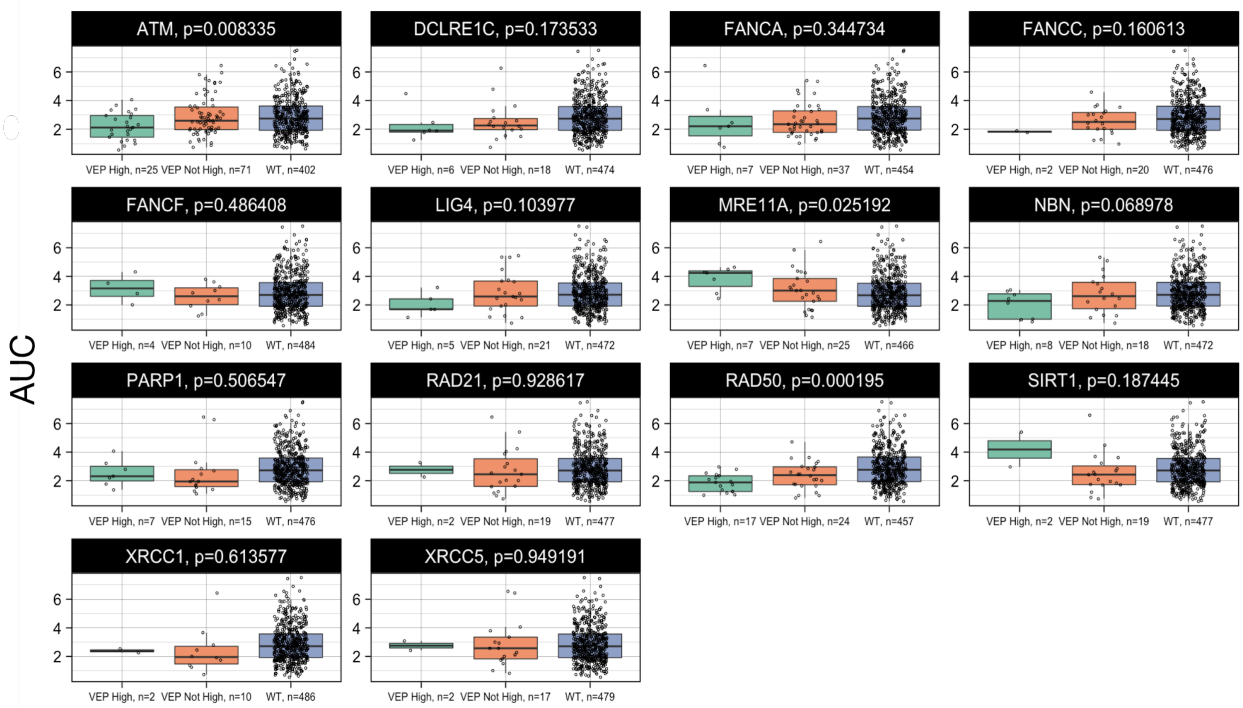
Supplementary Figure 3: Goodness of fit of the LQ model. A. Histogram of Rsquared values of LQ model demonstrating cutoff for goodness of fit. B. Goodness of fit values stratified by histology are displayed as Tukey boxplots.



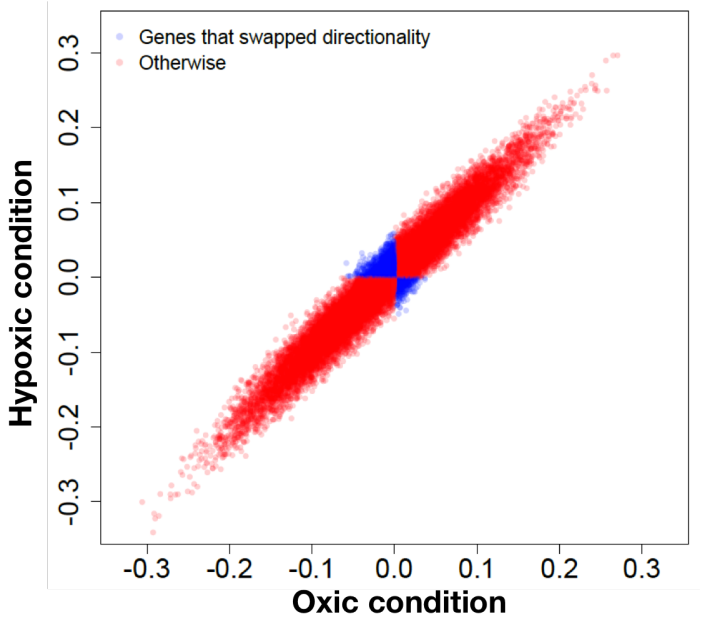
Supplementary Figure 4: Scatter plots of results between 9-day viability assay and clonogenic assay at individual response variables: (A) SF2; (B) SF4; (C) SF6; (D) SF8; (E) AUC. See Figure 1C for Pearson R and standard deviation values.



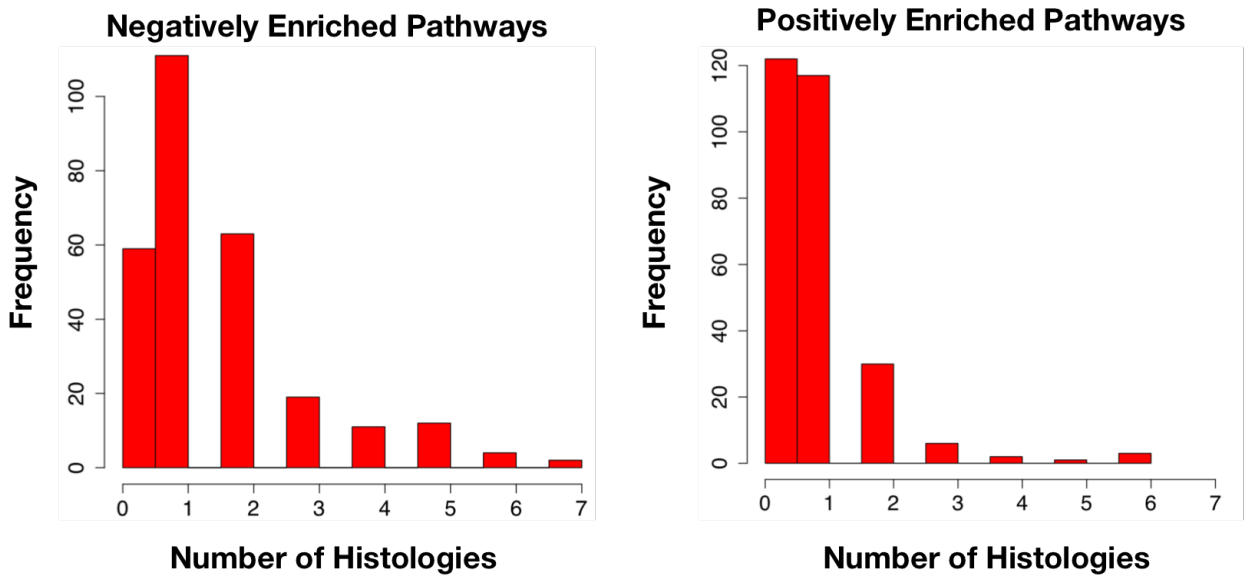
Supplementary Figure 5: Functional breakdown of pathway enrichment using SF2 and AUC vs AUC alone response variables. Groups were manually curated. Number of common pathways between SF2 and AUC are 35 (left panel) and the number of pathways unique to AUC are 42 (right panel). See Supplementary File 1 for full details.



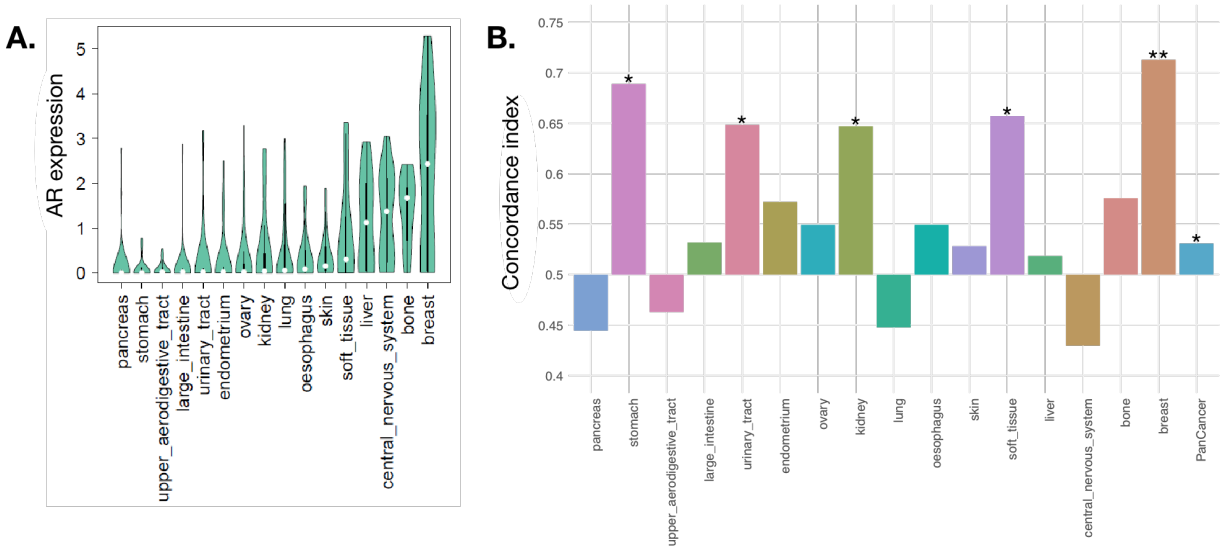
Supplementary Figure 6: Individual gene associations between DNA repair genes and radiation response. 14 genes implicated in NHEJ were assessed for mutations using CCLE data. Predicted functional impact of mutations was annotated using VEP. For each individual gene, box plots show radioresponse (AUC) of the cell lines grouped according to VEP-derived functional annotation. Wilcoxon-U p-values were determined by comparing 'VEP High' and 'WT' groups. With Bonferroni correction for multiple testing, VEP high mutations in RAD50 remain significantly associated with radiation sensitivity ($p<0.05$) with an adjusted $p=0.0027$.



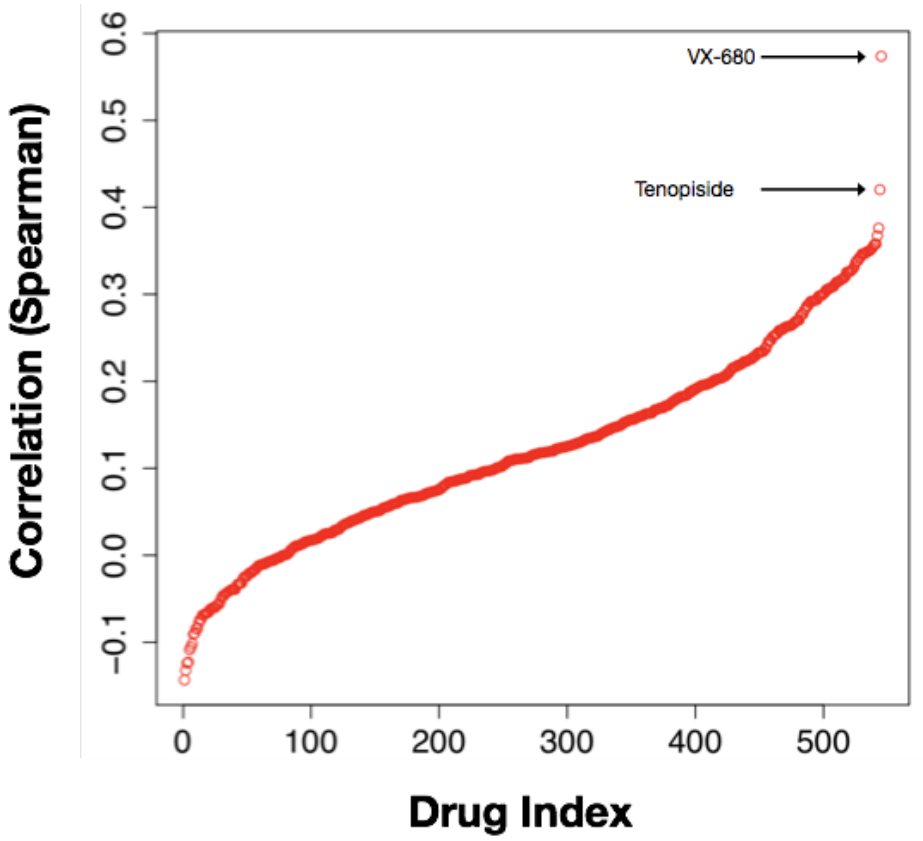
Supplementary Figure 7: Univariate correlation between radiation response associated genes under oxic and modeled hypoxic conditions.



Supplementary Figure 8: Histogram showing the number of cancer histologies significantly associated per pathway.



Supplementary Figure 9: Association between AR gene expression and Yard-AUC. (A) Box plot of AR expression across tumor histologies (those represented by >15 cell lines in RadioGx) showing a wide range within and across tissue types. **(B)** Concordance Index of AR and AUC (** indicates a q value<0.05 and * indicates a q value<0.25).



Supplementary Figure 10: Replication of Figure 1 from Yard et al 2016, demonstrating the correlation between drug response and radiation response. This figure was produced using the RadioGx package.

Supplementary Table 1: List of sensitivity and transcriptomic data sets integrated with RadioGx and used for this study

Name	Data Type	Reference
Yard	Radiation Sensitivity	(Yard et al., 2016)
Cancer Cell Line Encyclopedia (CCLE)	Drug Sensitivity and Transcriptomic	(Barretina et al., 2012)
Cancer Therapeutics Response Portal (CTRPv2)	Drug Sensitivity	https://ocg.cancer.gov/programs/ctd2/data-portal

Supplementary Table 2: Functionality of RadioGx package.

Function	Summary
linearQuadraticModel	Fit the dose response data using LQ model
OERmodel	Effect of oxygen using the Alper-Howard-Flanders model
computeAUC	Calculates the AUC of the LQ model fit
computeD10	Calculates the dose at which 10% of cells survive
computeSF2	Computes the SF2 for a given dose response data
doseresponsecurve	Plots the dose response curve

Supplementary Table 3: Rationale for positive control mutation gene

	Positive control genes for DNA repair		
	Gene	Prior publications indicating association with radiation response (PMID)	Notes
1	PARP1	20409643	
2	ATM	2725446	
3	XRCC6	18374504 and 19251090	Excluded - no VEP High mutations
4	LIG3	17889263	Excluded - no VEP High mutations
5	LIG4	2725446 and 15279811	
6	MRE11A	21227757	
7	NBN	2725446	
8	PRKDC	19797196	Excluded - no VEP High mutations
9	WRN	16394631	Excluded - no VEP High mutations
10	XRCC1	2925273 and 16829685	
11	XRCC4	26255102	
12	XRCC5	7739608	
13	RAD50	2681000	
14	DCLRE1C	15279811	
15	SIRT1	18374504	
16	RAD21	11483345	
17	FANCC	2725446	
18	FANCA	2725446	
19	FANCF	2725446	